REMARKS

Support for the amendments

The amendment to the specification reconciles the § 120 priority claim with the filing papers and § 1.63 declaration in this application and updates the status for the other listed applications. The title and abstract are revised to correspond to the claimed subject matter.

The references in the claims to residues 23 to 128 of SEQ ID NO: 4 and residues 20 to 140 of SEQ ID NO: 6 are supported by the disclosure as filed. The figures as filed identify the predicted signal peptide cleavage sites as recited in the amended claims. The disclosure as filed conveys to the skilled worker that cleavage of the propeptides as indicated is expected in the expression systems of the invention. The claims recite the portions of SEQ ID NOs: 4 and 6 corresponding to positions +1 to +107 of the light chain variable region and positions +1 to +113 of the heavy chain variable region as shown in Figures 4 and 5, respectively.

Support for "immunologically active" anti-CD20 antibodies is found, *e.g.*, at page 13, lines 12-16; and for "chimeric" antibodies, *e.g.*, at page 12, line 27. The recitation of kappa light chain and gamma 1 heavy chain constant regions is found, *e.g.*, at page 20, lines 9-10; page 21, lines 13-14; and line 17. Support for the recitation of the host cells in claims 70-75 is found, *e.g.*, at page 24, lines 1-2; page 24, lines 6 and 15; and page 42, lines 13-14.

The method for expressing and purifying anti-CD20 antibody as claimed in claim 76 is supported, *e.g.*, at page 19, line 22 to page 20, line 5; page 24, lines 1-26; page 42, line 28 to page 43, line 5. The recitation of "pharmaceutical carrier" and "pharmaceutically acceptable buffer" in claims 77, 78, 82, and 84 is supported, *e.g.*, at page 14, paragraph bridging to 15.

The claims to methods of using antibodies are supported generally, *e.g.*, at page 9, lines 10-17. Particular limitations in such claims have exemplary support in the specification as follows. Antibodies "not conjugated to a toxin or radioisotope" are supported, *e.g.*, at page 12, line 9. The recitation of "human light chain constant region and a human gamma 1 heavy chain constant region" is supported, *e.g.*, at page 20, lines 9-10 and page 21, lines 13-14 and 17.

Therapeutically effective dosages from 100 mg/m^2 to 500 mg/m^2 are described, *e.g.*, at page 57, lines 4-9. Applicant notes that this dosage range would cover at least the administration of fixed-dose formulations containing, *e.g.*, about 200 to about 900 mg of antibody for most patients.[1]

Treatment over a period of about 2 to 10 weeks is supported, *e.g.*, at page 16, lines 10-15. The specific treatment of claim 92 is described, *e.g.*, at page 57, line 27 to page 58, line 1. Depletion of peripheral B cells in excess of 2 weeks is supported, *e.g.*, at page 57, lines 1-2. Antibodies having the specificity of murine monoclonal antibody 2B8 as recited in claims 86 and 93 are described, *e.g.*, at page 43, lines 8-9 and page 43, lines 10 and 16-20. The ATCC deposit of the 2B8 hybridoma is cited at page 62, lines 16-29.

Treatments comprising the administration of chemotherapeutic agents are described, *e.g.*, at page 61, lines 22-28. The agents recited in claim 96 are identified, *e.g.*, at page 62, line 1. The recitation of treating relapsed B cell lymphoma in claim 97 is supported, *e.g.*, at page 56, line 17.

The amendments at pages 16 and 26 correct obvious informalities and identify trademarked names.

The amendments add no new matter to the disclosure.

Drawing correction

A substitute sheet for Figure 5 is attached. The correction involves the rectification of a typographical error in the amino acid sequence of the heavy chain variable domain of chimeric antibody C2B8. In particular, the predicted translation is corrected to indicate that the residue at position +14 is Pro, not Ala.

The nucleotide sequence in the figure as filed is correct. The codon corresponding to position +14 (CCT) in fact encodes the amino acid proline (Pro), not alanine (Ala) as shown in the figure. This is evidenced by the attached table showing the amino acids encoded by DNA

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[1] Based on conversions from mg/m^2 to mg dosages for an "average" 70 kg, 67 inch human.

codons, copied from the textbook by Lodish *et al.*, *Molecular Cell Biology*, available online at the PubMed website at the U.S. National Library of Medicine. (Note that this table lists U instead of T, reflecting the codons employed in RNA sequences.)

The correction is supported by the present application as filed and by the evidence in the priority applications. The following evidence supports the correctness of the nucleotide sequence and the assignment of residue +14 of the heavy chain at Pro instead of Ala.

- First, Figure 3, which provides the complete nucleotide sequence of the TCAE-8 vector, shows the same nucleotide sequence as Figure 5 in the region of interest. A copy of the relevant part of that figure from U.S. Patent No. 5,736,137 with the CCT codon boxed is attached.

- Second, the nucleotide sequence shown in the original sequence listing as SEQ ID NO: 3 (now SEQ ID NO: 5 in this application) is correct. The sequence listing was present in the application as filed.

- Third, the corresponding Fig. 5 from the original application in this series, U.S. application serial no. 07/978,891, shows the same nucleotide sequence and the correct predicted amino acid sequence (*i.e.*, including a Pro residue at position +14). The '891 application is incorporated by reference into this application. A copy of the figure from that application indicating residue +14 is also attached.

- Finally, the undersigned states that he has reviewed information, believed to be correct, indicating that the nucleotide sequence in the deposited clone, ATCC 69119, does in fact encode a Pro residue at position +14 of the heavy chain.

The error in Figure 5 of the application as filed is an "obvious error" that can be properly corrected on the evidence of record. Because the CCT codon always encodes a Pro amino acid residue, the skilled worker would immediately recognize that an error was present. Importantly, the skilled worker would also immediately understand what the correction must be. Also, the evidence in the patent application and in the priority document fully supports correcting the figure to show a Pro residue at position +14 in the amino acid sequence.

Corrected sequence listing

A substitute sequence listing accompanies this paper. The sequence listing is revised to reflect the correction to the amino acid sequence shown in Figure 5 (SEQ ID NO: 6) as discussed immediately above. Except for this correction, the sequences in the new sequence listing are identical to the sequences in the application as filed. For the reasons discussed in connection with the correction of the figure, applicant submits that this amendment adds no new matter.

A computer-readable copy of the attached sequence listing is filed with this amendment on compact disc. In compliance with 37 C.F.R. § 1.821(e), the undersigned states that the paper and computer-readable copies of the sequence listing are identical.

Conclusion

Applicant believes that this application is in condition for examination and requests that the examiner prepare an action on the merits at an early date.

Respectfully submitted,

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Table 4-2. The Genetic Code (RNA to Amino Acids)*

First Position (5′ end)	Second Position: U	Second Position: C	Second Position: A	Second Position: G	Third Position (3′ end)
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop (och)	Stop	A
	Leu	Ser	Stop (amb)	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu (Met)	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met (start)	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val (Met)	Ala	Glu	Gly	G

*"Stop (och)" stands for the ochre termination triplet, and "Stop (amb)" for the amber, named after the bacterial strains in which they were identi-

ANNOTATED SHEET

HUMAN KAPPA CONSTANT=324bp=107 AMINO ACID & STOP CODON
CTCCAATCGG GTAACTCCCA GGAGAGTGTC ACAGAGCAGG ACAGCAAGGA CAGCACCTAC 1560

AGCCTCAGCA GCACCCTGAC GCTGAGCAAA GCAGACTACG AGAAACACAA AGTCTACGCC 1620

TGCGAAGTCA CCCATCAGGG CCTGAGCTCG CCCGTCACAA AGAGCTTCAA CAGGGGAGAG 1680

STOP
LIGHT
CHAIN Eco RI LINKER #4=81bp
TGTTGAATTC AGATCCGTTA ACGGTTACCA ACTACCTAGA CTGGATTCGT GACAACATGC 1740
1646 7

GGCCGTGATA TCTACGTATG ATCAGCCTCG ACTGTGCCTT CTAGTTGCCA GCCATCTGTT 1800
1771 2

GTTTGCCCCT CCCCCGTGCC TTCCTTGACC CTGGAAGGTG CCACTCCCAC TGTCCTTTCC 1860

TAATAAAATG AGGAAATTGC ATCGCATTGT CTGAGTAGGT GTCATTCTAT TCTGGGGGGT 1920

BOVINE GROWTH HORMONE POLYADENYLATION REGION=231bp
GGGGTGGGGC AGGACAGCAA GGGGGAGGAT TGGGAAGACA ATAGCAGGCA TGCTGGGGAT 1980

LINKER #5=15bp
GCGGTGGGCT CTATGGAACC AGCTGGGGCT CGACAGCTAT GCCAAGTACG CCCCCTATTG 2040
2002 3 2017 8

ACGTCAATGA CGGTAAATGG CCCGCCTGGC ATTATGCCCA GTACATGACC TTATGGGACT 2100

TTCCTACTTG GCAGTACATC TACGTATTAG TCATCGCTAT TACCATGGTG ATGCGGTTTT 2160

CMV PROMOTER-ENHANCER=334bp
GGCAGTACAT CAATGGGCGT GGATAGCGGT TTGACTCACG GGGATTTCCA AGTCTCCACC 2220

CCATTGACGT CAATGGGAGT TTGTTTTGGC ACCAAAATCA ACGGGACTTT CCAAAATGTC 2280

GTAACAACTC CGCCCCATTG ACGCAAATGG GCGGTAGGCG TGTACGGTGG GAGGTCTATA 2340

LINKER #6=7bp Sal I
TAAGCAGAGC TGGGTACGTC CTCACATTCA GTGATCAGCA CTGAACACAG ACCCGTCGAC 2400
START 2351 2 2358 9

HEAVY CHAIN SYNTHETIC & NATURAL LEADER Mlu I 2457 8
ATGGGTTGGA GCCTCATCTT GCTCTTCCTT GTCGCTGTTG CTACGCGTGT CCTGTCCCAG 2460
2401 -5 -4 -3 -2 -1 +1

GTACAACTGC AGCAGCCTGG GGCTGAGCTG GTGAAGCCTG GGGCCTCAGT GAAGATGTCC 2520

TGCAAGGCTT CTGGCTACAC ATTTACCAGT TACAATATGC ACTGGGTAAA ACAGACACCT 2580

HEAVY CHAIN VARIABLE=363bp=121 AMINO ACID
GGTCGGGGCC TGGAATGCAT TGGAGCTATT TATCCCGGAA ATGGTGATAC TTCCTACAAT 2640

CAGAAGTTCA AAGGCAAGGC CACATTGACT GCAGACAAAT CCTCCAGCAC AGCCTACATG 2700

CAGCTCAGCA GCCTGACATC TGAGGACTCT GCGGTCTATT ACTGTGCAAG ATCGACTTAC 2760

TACGGCGGTG ACTGGTACTT CAATGTCTGG GGCGCAGGGA CCACGGTCAC CGTCTCTGCA 2820

Nhe I
GCTAGCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCT CCTCCAAGAG CACCTCTGGG 2880

GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCG 2940

HUMAN GAMMA 1 CONSTANT=993bp
TGGAACTCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCCT ACAGTCCTCA 3000

FIG. 3B

ANNOTATED SHEET

07 978891

mHvy

FIGURE 5

Leader

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          -19             -15             -10              -5
Frame 1   Met Gly Trp Ser Leu Ile Leu Leu Phe Leu Val Ala Val Ala Thr Arg Val
          ATG GGT TGG AGC CTC ATC TTG CTC TTC CTT GTC GCT GTT GCT ACG CGT GTC
                2409        2418        2427        2436        2445

      -1| +1      FR1                             10                  15
Leu Ser| Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala Ser
CTG TCC| CAG GTA CAA CTG CAG CAG CCT GGG GCT GAG CTG GTG AAG CCT GGG GCC TCA
       2460        2469        2478        2487        2496        2505

            20                  25                  30| 31  CDR1      35 |36
Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr |Ser Tyr Asn Met His |Trp
GTG AAG ATG TCC TGC AAG GCT TCT GGC TAC ACA TTT ACC |AGT TAC AAT ATG CAC |TGG
       2517        2526        2535        2544    |   2553        2562 |

              40 FR2              45              49 |50      52 52A  53  54
Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly |Ala Ile Tyr Pro Gly Asn
GTA AAA CAG ACA CCT GGT CGG GGC CTG GAA TGG ATT GGA |GCT ATT TAT CCC GGA AAT
       2574        2583        2592        2601    |   2610        2619

55          CDR2     60                 65 |66 FR3         70
Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly |Lys Ala Thr Leu Thr Ala Asp Lys
GGT GAT ACT TCC TAC AAT CAG AAG TTC AAA GGC |AAG GCC ACA TTG ACT GCA GAC AAA
       2631        2640        2649        2658        2667        2676

   75                  80      82  82A 82B 82C 83      85
Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
TCC TCC AGC ACA GCC TAC ATG CAG CTC AGC AGC CTG ACA TCT GAG GAC TCT GCG GTC
       2688        2697        2706        2715        2724        2733

90              94| 95      CDR3       100 100A 100B 100C 100D 101 |102 103
Tyr Tyr Cys Ala Arg| Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val |Trp Gly
TAT TAC TGT GCA AGA| TCG ACT TAC TAC GGC GGT GAC TGG TAC TTC AAT GTC |TGG GGC
       2745        2754        2763        2772        2781        2790

105 FR4         110         113
Ala Gly Thr Thr Val Thr Val Ser Ala
GCA GGG ACC ACG GTC ACC GTC TCT GCA
       2802        2811        2820
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